Antiviral, Antifungal and Antiamoebic and other Antiprotozoal Drugs

Antiviral Agents

Viruses have no cell wall and made up of nucleic acid core enclosed in a protein coat which consists of identical subunits.

Viruses are of two types:

1- **DNA (deoxyribonucleic acid) viruses:** DNA viruses are herpes simplex, small pox, hepatitis B, varicellazoster etc.

2- **RNA (ribonucleic acid) viruses:** RNA viruses are rabies, measles, dengue, rubella, yellow fever, poliomyelitis and HIV etc.

In viral infections, replication of viruses are at peak, at or before the manifestation of clinical symptoms. So, the treatment generally depends either on early initiation of therapy or prevention of infection i.e. chemoprophylaxis.

The various antiviral agents are classified as under (the doses for specific infections is given in text) in table 9.6.1.

Table 9.6.1: *Classification of antiviral agents.*

I.	**Antiherpes agents**
	Idoxuridine (RIDINOX)
	Acyclovir (ZOVIRAX)
	Famciclovir (FAMTRAX)
	Valacyclovir
	Ganciclovir
II.	**Antiretroviral agents**
a.	***Nucleoside reverse transcriptase inhibitors***
	Zidovudine (RETROVIR)
	Lamivudine (HEPITEC)
	Stavudine (STAVIR)
	Didanosine (DINEX)
b.	***Nonnucleoside reverse transcriptase inhibitors***
	Nevirapine (NEVIMUNE)
	Efavirenz (EFAVIR)
c.	***Retroviral protease inhibitors***
	Indinavir (INDIVIR)
	Ritonavir
	Saquinanir
	Nelfinavir
III.	**Antiinfluenza virus agents**
	Amantadine
	Rimantadine
	Zanamavir
	Ribavarin (RIBAVIN)
	Interferons

A- ANTI-HERPES AGENTS

1- Idoxuridine (RIDINOX)

It is chemically related to thymidine and acts by competing with it in the synthesis of DNA and ultimately preventing the utilization of thymidine. It prevents the replication of DNA viruses and its clinical use is limited to herpes simplex keratitis. **Toxicity** includes alopecia, leucopenia, thrombocytopenia and liver damage.

It is used in herpes simplex keratoconjunctivitis in 0.1 to 0.5% solution/eye oint ment applied one to two hourly.

2- Acyclovir (ZOVIRAX)

Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses. Acyclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

Acyclovir is only partially (20%) absorbed from the gut.

Most of the drug is excreted un changed by the kidney by tubular secretion and glomerular filtration. 9-Carboxymethoxymethylguanine is the only significant metabolite of acyclovir recovered from the urine.

Adverse reactions include nausea, vom iting, fatigue, diarrhoea and abdominal pain, rashes including photosensitivity, urticaria, pruritus, increase in blood urea and creatinine, reversible rise in bilirubin and liverrelated en zymes. Neurological adverse effects are headache, dizziness, confusional state, hallu cinations, somnolence and convulsions.

Indications

- Treatment of herpes simplex virus infection of the skin and mucous membrane, including initial and recurrent genital herpes.
- For the prevention of recurrences of herpes simplex infection in immuno competent patients.
- Prophylaxis of herpes simplex infection in immunocompromised patients.
- Treatment of varicella (chickenpox) and herpes zoster (shingles) infections. Early treatment of shingles with acyclovir can reduce the incidence of post-herpetic neuralgia (zosterassociated pain).

Dosage

- **Dosage for treatment of herpes simplex in adults:** 200 mg five times daily for five days. In severely immunocompromised patients or in patients with impaired absorption from the gut the dose can be doubled to 400 mg or IV dose can be given.

- **Dosage for suppression of herpes simplex in adults:** In immunocompetent patients, 200 mg four times daily six hourly.
- **Dosage for prophylaxis of herpes simplex in adults:** 200 mg four times daily at six hourly intervals. In severely immunocompromised patients or in patients with impaired absorption from the gut the dose can be doubled to 400 mg or IV dosing can be given.
- **Dosage for treatment of varicella and herpes zoster in adults:** 800 mg five times daily four hourly intervals for seven days. IV dose can be given in severely immunocompromised patients or in patients with impaired absorption from the gut.
- **Dosage for management of severely immunocompromised patients:** 800 mg four times daily at six hourly intervals.

3- Famciclovir (FAMTRAX)

Famciclovir is an orally administered prodrug of the antiviral agent penciclovir. Famciclovir is indicated for the treatment of acute herpes zoster (shingles), treatment or suppression of recurrent genital herpes in immunocompetent patients, treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

Adverse reactions are headache, paresthesia, migraine, nausea, diarrhoea, vomiting, flatulence, abdominal pain, fatigue, pruritus, rash and dysmenorrhoea.

DOSAGE AND ADMINISTRATION

Herpes Zoster

- Immunocompetent patients**:** 750 mg once daily for 7 days or 250 mg every 8 hours for 7 days.
- Immunocompromised patients: 500 mg three times daily for 10 days. Famciclovir should be initiated immediately upon diagnosis of herpes zoster, preferably within 48 hours of the onset of the rash.

Genital Herpes

First episode of genital herpes:

- Immunocompetent patients: 250 mg famciclovir three times daily for 5 days, initiated as soon as possible after lesion onset.
- Immunocompromised patients: 500 mg twice daily for 7 days.

Episodic treatment of recurrent genital herpes:

- Immunocompromised patients: 125 mg twice a day for 5 days.

Acute recurrent genital herpes infection:

- Immunocompromised patients: 500 mg twice daily for 7 days.

Suppressive treatment of recurrent genital herpes:

- Immunocompetent patients: 250 mg BD for up to one year.

• In HIV-infected patients: Famciclovir is to be given 500 mg BD orally.

4- Valacyclovir

It is the L-valyl ester of acyclovir and rapidly converted into acyclovir after oral administration. Its mechanism of action and pharmacokinetics are similar to acyclovir.

In genital herpes dose required is 1 g BD for 10 days and on recurrence 500 mg BD for 5 days.

For herpes zoster infection 1 g TDS for 7 days is required.

Dose of 2 g QID has also been used in preventing cytomegalovirus (CMV) disease after organ transplantation.

5- Ganciclovir

It is an acyclic guanosine analog which require triphosphorylation for activation prior to inhibition of viral DNA polymerase. It is active against cytomegalovirus (CMV), varicellazoster virus, Epstein-Barr virus and human herpes virus-8. It is almost 100 times more potent than acyclovir against CMV.

Its use is restricted in severe CMV infections in immunocompromised especially CMV retinitis, CMV pneumonia or colitis.

B- ANTI-RETROVIRAL AGENTS

1- Zidovudine (RETROVIR)

It is a thymidine analogue. After phosphorylation in body zidovudine triphosphate selectively inhibits viral reverse transcriptase i.e. RNA dependent DNA polymerase. It is effective against retrovirus only. It has rapid oral absorption and 65% bioavailability. It can cross the placenta. It is eliminated primarily by renal excretion following glucuronidation in the liver.

Adverse effects include anorexia, nausea, headache, abdominal pain, myalgia, anaemia insomnia, neutropenia, convulsions and encephalopathy.

It is used in asymptomatic and symptomatic HIV disease in a dose range of 200 mg six times a day on initial basis and thereafter upto 500 to 1500 mg daily in four to five divided doses.

2- Lamivudine (HEPITEC)

It is synthetic nucleoside analogue active against HIV. It is phosphorylated to its active 5'-triphosphate metabolite (L-TP). Lamivudine triphosphate inhibit HIV reverse transcription via viral DNA chain termination. It is rapidly absorbed after oral administration. The major part of the dose is excreted in unchanged form in urine.

Adverse effects include pancreatitis with symptoms of nausea, vomiting, severe abdominal or stomach pain and is more frequent in children. Paresthesia and

peripheral neuropathy with tingling, burning, numbness or pain in the hands and feet are also more frequent in children.

Lamivudine may be used prophylactically in health care workers at risk of acquiring HIV infection after occupational exposure to the virus and in combination with zidovudine for treatment of HIV infection.

It is to be given in a dose of 150 mg BD in combination with zidovudine (in children 4 mg/kg BD, max 150 mg BD).

3- Stavudine (STAVIR)

It is synthetic thymidine nucleoside analogue, active against HIV. Stavudine rapidly enters cells by diffusion. Stavudine triphosphate acts as a competitive inhibitor of reverse transcriptase with respect to deoxythmidine triphosphate and incorporation causes termination of DNA chain elongation. It inhibits replication of HIV in human cells. It is rapidly absorbed after oral administration. Approximately 40 percent of stavudine appears unchanged in the urine through tubular secretion and glomerular filtration. Nonrenal clearance mechanisms account for about 50 percent of elimination of a dose.

Adverse effects include peripheral neuropathy which is a major clinical toxicity. Other side effects include pancreatitis, anaemia, arthralgia, headache, fever, rash, nausea, vomiting, diarrhoea, elevated transaminase values.

It is indicated in the treatment of advanced HIV infection in a dose range 30 to 40 mg BD.

4- Nevirapine (NEVIMUNE)

It is non-nucleotide reverse transcriptase inhibitor extensively metabolized by the CYP3A P450 isoform to hydroxylated metabolites and excreted in urine.

It is indicated in combination with other anti-retroviral agents in a dose of 200 mg OD-BD for first 14 days. It is also been shown to be effective in the prevention of transmission of HIV from mother to new born.

The serious side effect is life threaten ing rash including Stevens Johnson syndrome and rarely toxic epidermal necrolysis. Other side effects are hepatitis, nausea, vomiting, fatigue, fever, headache, hypersensitivity reactions, urticaria, an gioedema and anaphylactic shock.

5- Efavirenz (EFAVIR)

It is also an non-nucleotide reverse transcriptase inhibitor having long half-life (40-55 hrs) and administered once daily. It is metabolized by CYP3A4 and CYP2B6 to inactive hydroxylated metabolites and eliminated in feces. It is used in combination with other retroviral drugs for the treatment of HIV infection in a dose of 600 mg once daily.

Adverse effects include drowsiness, insomnia, dizziness, agitation, confusion, depression, delusions, vomiting, diarrhoea, crystalluria, elevation in liver enzyme and total serum cholesterol. Serious side effect is skin rash including Stevens Johnson syndrome as in case of nevirapine.

6- Indinavir (INDIVIR)

It is an inhibitor of the enzyme HIV protease which is required for the pro teolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV. Indinavir binds to the protease active site and inhibits the activity of the enzyme HIV protease preventing cleavage of the viral polyproteins resulting in the formation of immature noninfectious viral particles.

Adverse effects include nausea, vomiting, diarrhoea, abdominal discomfort, dry mouth, taste disturbances; headache, dizziness, insomnia; myalgia, rash, pruritus, dry skin, hyperpigmentation, nephrolithiasis, dysuria, haematuria, crystalluria, proteinuria; elevated liver enzymes and bilirubin, hepatitis; neutropenia, haemolytic anaemia and hyperglycaemia etc.

It is indicated in treatment of HIV infection and is used in combination with other anti-retroviral agents in a dose 800 mg every eight hourly.

7- Ritonavir

It is inhibitor of HIV-1 and 2 proteases. **The common adverse effects** include GIT disturbances, hypertriglyceridemia and elevation of serum aminotransferase.

C- ANTI-INFLEUNZA VIRUS AGENTS

1- Amantadine

It exerts its action by inhibiting the replication of influenza virus, by inhibiting uncoating of viral RNA of influenza A within infected host cells. It is used in a dose of 200 mg/day in prevention of influenza A virus infection. After oral administration, it is excreted unchanged in urine.

Adverse effects include confusion, insomnia, anxiety, hallucinations, skin rash and retention of urine.

It is used in prophylaxis of influenza A virus, idiopathic parkinsonism and drug induced extrapyramidal reactions.

2- Rimanditine

Rimanditine is a more potent and longer acting congener of amantadine.

3- Ribavarin (RIBAVIN)

It is a guanosine analog which probably interferes with the synthesis of guanosine triphosphate, inhibiting capping of viral mRNA and to inhibit the viral RNA-

dependent RNA polymerase. Orally absorbed and bioavailability is about 50%. It is partly metabolized and eliminated in a multiexponential manner.

Adverse reactions include anaemia, gastrointestinal disturbances, headache and haemolysis.

It is active against influenza A and B, measles, paramyxoviruses, respiratory syncytial virus, HCV and HIV-1 in a dose of 200 mg four times per day.

4- Interferons

Interferons are cellular glycoproteins produced by the host cells which exert complex antiviral, immunoregulatory and antiproliferative activities. After binding to interferon receptors it acts through cellular metabolic processes which involves synthesis of viral RNA and proteins. Interferon receptors are tyrosine protein kinase receptors which on activation phosphorylate cellular proteins. These then induce transcription of 'interferon induced proteins' which exert antiviral effects. There are three type of interferons: **alpha**, **beta** and **gamma**.

Interferons are indicated in chronic hepatitis B and C in a dose of 10 MU injection three times a week for six months.

Alpha interferon is also effective in the treatment of hairy cell leukaemia, condyloma acuminata (caused by papilloma virus), chronic myelogenous leukaemia and AIDS related Kaposi's sarcoma. Interferons are not effective orally and is used only by IM or SC injection.

Adverse effects include fever, leucopenia, thrombocytopenia, alopecia, neurotoxicity and elevated aminotransferase levels. Other less common side effects include hypotension, cardiomyopathy and hyperglycaemia.

Antifungal Agents

Antifungal agents are used in the treatment of topical and systemic fungal infection. They can be classified as systemic or topical antifungal agents and some are used both systemically as well as topically in the form of powder, ointment and vaginal tablets etc. They are classified as in table 9.7.1.

A-ANTIFUNGAL ANTIBIOTICS

1- Amphotericin-B (FUNGIZONE)

It is an antifungal antibiotic obtained from Streptomyces nodosus and chemically it is an amphoteric polyene macrolide. It has a highly double bonded structure. The cell membrane sterol 'ergosterol' is found in the cell membrane of fungi and the predominant sterol of bacteria and human cell is cholesterol. This antifungal antibiotic binds to ergosterol which alters the permeability of the cells by forming

amphotericin-B associated pores in cell membrane, which allows the leakage of intracellular ions and macromolecules which can lead to cell death.

Amphotericin B has a wide spectrum of antifungal activity. It is active against *Histoplasma capsulatum, Cryptococcus neoformans, Candida albicans, Sporotrichum schenkii, Blastomyces brasiliensis, Coccidioides immitis, Rhodotorula, Aspergillus* etc. It is fungicidal at high and fungistatic at low concentration.

It is poorly absorbed from GIT and topically. After IV administration it is widely distributed in tissues. About 60% drug is metabolized in liver and excretion occurs slowly both in urine and bile.

Adverse effects include nausea, vomiting, headache, fever, breathlessness, anaemia, thrombophlebitis on IV administration. On long term use, dose related nephrotoxicity and anaemia occurs.

It is used orally for intestinal candidiasis, topically for oral, vaginal and cutaneous candidiasis and hospital treatment of progressive and potentially fatal systemic fungal infections. It is the gold standard of antifungal therapy. Flucytosine has supraadditive action with amphotericin B if the fungi is sensitive to both. It is also potentiated by rifampicin and minocycline

Table 9.7.1: *Classification of antifungal agents.*

I. **Antifungal antibiotics**	
Amphotericin-B (FUNGIZONE)	50-100 mg QID, 200 µg to 1.5 mg/kg daily or on alternate days IV infusion, 3% topical (ear drops)
Nystatin (MYCOSTATIN)	5 lac U orally TDS, 1 lac U topical (ointment vaginal tablet)
Griseofulvin (DERMONORM)	0.5-1.0 g/day
Pimaricin	Topical (2% cream, 25 mg vaginal tablet, 5% ophthalmic ointment)
Hamycin	2-5 lac U (suspension & topically as vaginal tablet and ointment)
II. **Antimetabolite**	
Flucytosine (ALCOBON)	100-150 mg/kg/day
III. **Imidazoles & triazoles**	
Clotrimazole (CLOTRIN)	100 mg vaginal tablet, 1% topical (lotion, cream and powder)
Ketoconazole (NIZRAL)	200 mg OD-BD orally, topical 2% ointment and shampoo
Miconazole (DAKTARIN)	3-15 mg/kg with glucose & saline IV infusion, 1-2% topical (powder, lotion, vaginal gel, ointment & vaginal ovules)
Econazole	150 mg vaginal tablet, 1% topical (cream & ointment)
Itraconazole (CANDITRAL)	100-200 mg/day (the number of days depend upon the type of infection)
Fluconazole (FLUZON) Also used with tinidazole (AZOSTAT)	400 mg on 1st day, then 200-400 mg OD, for 28 days,
Terbinafine (LAMISIL)	250 mg OD for 6-12 wks.
IV. **Miscellaneous agents (used topically)**	
Tolnaftate (TINADERM)	1% solution cream
Selenium sulfide (SELSUN)	Shampoo
Cyclopirox olamine	1% solution, skin cream & vaginal cream
Benzoic acid	3-5% skin ointment
Sodium thiosulfate	20% solution
Quiniodochlor	3-8% skin cream

2- Nystatin (MYCOSTATIN)

It is obtained from Streptomyces noursei. It has similar antifungal action as amphotericin but is highly toxic and used topically only.

It is effective against *Candida, Histoplasma, Trichophyton, Blastomyces, Microsporum audouini* etc. It is indicated in *Candida albicans* especially oral moniliasis, monilial vaginitis, conjunctival, cutaneous and corneal candidiasis.

3- Griseofulvin (DERMONORM)

It is isolated from Penicillium griseofulvium. It is active against Epidermophyton, Trichophy ton and Microsporum causing superficial infection or dermatophytosis.

It is not effective against fungi causing deep/systemic infection. It interferes with mitosis and also causes abnormal metaphase configurations. Griseofulvin gets deposited in keratin and persists for weeks. As it is fungi static the newly formed keratin is not invaded by the fungus but fungus persists in already infected keratin, till it is shed off.

Oral absorption is irregular. It is largely metabolized by methylation and excreted in urine. It is ineffective topically.

Adverse effects include nausea, epigastric distress, vomiting, headache, peripheral neuritis, skin rash, photosensitivity, drowsiness and transient leucopenia. It can cause disulfiram like reaction.

It is indicated in fungal infections of skin, scalp and nails, tinea of hand and beard and athlete's foot.

4- Pimaricin

It is obtained from Streptomyces notalensis and it is found effective against Trichophyton violaceum, *Trichomonas vaginalis* and *Aspergillus fumigatus*.

It is used as eye ointment in keratitis due to Fusarium and Cephalosporium and as an inhalation in bronchopulmonary aspergillosis and candidiasis.

5- Hamycin

It is obtained from *Streptomyces pimprina* and effective against *blastomycosis, cryptococcosis*, vaginal and cutaneous candidiasis, *Trichomonas vaginitis* and *Aspergillus otomycosis.*

Adverse effects include diarrhoea, eosinophilia, nephrotoxicity and rise in SGOT levels after oral administration in the treatment of blastomycosis in man.

B- ANTIMETABOLITES

1- Flucytosine (ALCOBON)

It is a synthetic fluorinated pyrimidine anti-metabolite which acts by its conversion to anti-metabolite 5-fluorouracil which inhibit DNA synthesis. It is

effective against Cryptococcus neoformans and some Candida strains and dermatiaceous moulds which cause chromoblastomycosis.

Adverse effects include anaemia, leukopenia, thrombocytopenia, diarrhoea, GIT disturbances and liver dysfunction.

It is mainly used as an adjuvant drug to amphotericin.

C- IMIDAZOLES & TRIAZOLES

1- Clotrimazole (CLOTRIN)

Clotrimazole, is an imidazole derivative and has a broad antimycotic spectrum of action in vivo, which includes dermato phytes, yeasts, moulds etc. Clotrimazole acts against fungi by in hibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

In addition, it also acts on *Trichomonas vaginalis*, gram positive microorganisms (*streptococci/staphylococci*) and gram negative microorganisms (Bacteroides/ *Gardnerella vaginalis*). It is useful as topical application.

It is indicated in infections of the genital region (vaginitis) caused by fungi (mostly Candida) and superinfections caused by clotrimazole sensitive bacteria; infectious leucorrhoea caused by yeast fungi.

It is well tolerated but some patients reported skin reactions including burning, stinging or redness.

2- Ketoconazole (NIZRAL)

It is orally effective broad spectrum imidazole antifungal drug. It is useful in both dermatophytosis and deep mycosis. Oral absorption is facilitated by gastric acidity. It is highly protein bound, metabolised in liver and metabolites are excreted in urine and faeces. Its spectrum is similar to that of miconazole and is more active against Coccidioides.

Adverse effects include gastric irritation, nausea, vomiting, headache, paresthesia, rash, hair loss, allergic reaction and gynecomastia.

3- Miconazole (DAKTARIN)

It has broad spectrum antifungal and antibacterial activity and is effective against *Cryptococcus*, *Blastomyces*, *dermatophytes*, *Microsporum*, *Coccidioides* and *Candida*. Used topically as ointment, lotion, gel, ear drop and vaginal gel. **Adverse effects** include fever, chills, allergic reaction and even anaphylaxis. It is indicated in *vulvovaginal candidiasis*, *Trichomonas vaginitis*, *otomycosis*, *tinea* and *Pityriasis versicolor*.

4- Econazole

It is similar to clotrimazole and is effective in dermatophytosis, otomycosis and oral thrush. It causes local irritation.

5- Itraconazole (CANDITRAL)

It is a triazole antifungal drug closely related to ketoconazole and is meant for oral use. It is very effective in a wide range of superficial and deep seated fungal infections. It impairs the synthesis of ergosterol in fungi.

After oral administration, it is widely distributed in the body. CSF and saliva contain negligible amounts of the drug. It is extensively metabolized in liver and the metabolites are excreted in urine. **It is indicated** in dermatophytoses, tinea versicolor, onychomycoses, oropharyngeal candidiasis, cutaneous candidiasis, chronic mucocutaneous candidiasis, oculomycoses; systemic mycoses like cryptococcosis, candidi asis and aspergillosis; subcutaneous mycoses like sporotrichosis and chromomycosis.

Adverse effects include nausea, vomiting, skin rash, depression, dizziness, vertigo and loss of libido, hypokalemia and hypertriglyceridemia.

6- Fluconazole (FLUZON)

It has broad range of antifungal activity. It is well absorbed orally (94%). It is primarily excreted unchanged in urine. Fungicidal concentration is achieved in nail, saliva and vagina and also penetrates brain.

Adverse effects include nausea, vomiting, headache, abdominal pain, diarrhea and skin rash.

It is indicated in mucosal candidiasis, systemic candidiasis, crypttococcosis, prophylaxis of fungal infections following cytotoxic chemotherapy or radiotherapy; maintenance to prevent relapse of cryptococcal meningitis in patients with AIDS; sporotrichosis, histoplasmosis and vaginal candidiasis.

7- Terbinafine (LAMISIL)

It is a synthetic allylamine derivative, which exerts its antifungal effect by inhib iting squalene epoxidase leading to de ficiency of ergosterol and corresponding accumulation of squalene which causes fungal cell death. It is well absorbed from the GI tract, widely distributed in body. It is strongly plasma protein bound. It is metabolized in the liver to inactive metabolites which are excreted in the urine.

Adverse effects are irritation, burning, itching and dryness on topical application. Oral intake causes gastric upset, rash, taste disturbance and hepatic dysfunction.

Terbinafine is used in the treatment of dermatophytoses especially onchomycosis by oral therapy. Also useful in tinea and pityriasis versicolor.

8- Miscellaneous agents (used topically)

1- Tolnaftate (TINADERM)

Tolnaftate is effective in tinea cruris and tinea corporis. Used in the form of solution and cream used topically. Not useful in candidiasis and other types of superficial mycoses. Adverse reaction includes local irritation.

2- Selenium sulfide (SELSUN)

Selenium sulfide is used as shampoo and used in the treatment of scalp fungal infection.

3- Cyclopirox olamine

Cyclopirox olamine is used in the treat ment of tinea infections, dermal and vaginal candidiasis.

4- Benzoic acid

Benzoic acid has got antifungal and anti-bacterial activity and used in combination with salicylic acid (Whitfield's ointment). Salicylic acid by its keratolytic action helps to remove the infected tissue and promotes the penetration of benzoic acid into the lesion.

5- Sodium thiosulfate

Sodium thiosulfate is effective against *Malassezia furfur*.

6- Quiniodochlor

Quiniodochlor is found effective against dermatophytosis, infected eczema and seborrhoeic dermatitis. Orally it is used as luminal amoebicide.

Antiamoebic and other Antiprotozoal Drugs

AMOEBIASIS

Amoebiasis is an infectious disease caused by Entamoeba histolytica. It can cause asymptomatic intestinal infection, colitis (mild to moderate), dysentery (severe intestinal infection), ameboma, liver abscess etc. The drugs used in chemotherapy of amoebiasis are classified as in table 9.9.1.

1- Metronidazole (FLAGYL)

It is a nitroimidazole. It has a broad spectrum of protozoal and antimicrobial activity. It shows antibacterial action against all anaerobic cocci, anaerobic gram negative bacilli including bacteroides species and anaerobic spore forming gram positive bacilli. It is very effective in infections due to *Entamoeba histolytica*, *Giardia lamblia* and *Trichomoniasis*. It also causes radio-sensitization. In shows selective toxicity to anaerobic microorganisms,

where it is converted to active form by reduction of its nitro group and this gets bound to DNA and prevent nucleic acid formation.

After oral administration it is rapidly and completely absorbed. It penetrates well into body tissues and fluids. It is metabolised in liver by oxidation and glucuronide conjugation and is excreted in urine.

Adverse effects include nausea, metallic taste, headache, dry mouth, abdominal distress, vomiting, diarrhoea, glossitis, stomatitis, vertigo, dizziness, ataxia, thrombophlebitis and very rarely convulsions. It shows disulfiram like effect.

It is drug of choice for all forms of amoebic infections used in *trichomonas vaginitis*, anaerobic postoperative infections, giardiasis, acute ulcerative gingivitis, H. pylori infection, pseudomem branous enterocolitis and anaerobic vaginosis.

Table 9.9.1: *Classification of drugs used in amoebiasis.*

I. **Imidazole derivatives**	
Metronidazole (FLAGYL)	
Amoebiasis	400-800 mg TDS for 5-10 days; 7.5-15 mg/kg IV infusion BD-QID
Trichomonas vaginitis	400 mg TDS × 7 days
Giardiasis	200 mg TDS × 3 days
Tinidazole (TINIBA)	
Amoebiasis	2 g OD × 3 days
Trichomoniasis and giardiasis	2 g OD
Secnidazole (SECNIL)	2 g single dose
Ornidazole (DAZOLIC)	500 mg BD × 5-7 days
II. **Quinoline derivative**	
Iodochlorohydroxyquin (ENTEROQUINOL)	250-500 mg TDS
Diiodohydroxyquin (DIODOQUIN)	650 mg TDS
Chloroquine	600 mg × 2 days then 300 mg OD × 2-3 wks
III. **Emetine derivatives**	
Dehydroemetine (TILEMETIN)	10-20 mg TDS × 6-10 days
Emetine, emetine bismuth iodide	
IV. **Miscellaneous**	
Diloxanide furoate (FURAMIDE)	500 mg TDS × 5-10 days
Furazolidone (FUROXONE)	100 mg TDS-QID × 5-7 days
Paromomycin	500 mg TDS × 5 days
Tetracycline	250 mg QID

2- Tinidazole (TINIBA)

It is similar to metronidazole and has long plasma half-life and given once daily. It is well absorbed after oral administration and penetrates well into the body tissues and fluids.

Incidence of side effects in lower. Side effects include nausea, epigastric discomfort, metallic taste, furred tongue, skin rash, urticaria and leucopenia.

It is indicated in giardiasis, amoebic liver abscess, intestinal amoebiasis, trichomoniasis, ulcerative gingivitis, treatment and prophylaxis of anaerobic infections. **It is also used** in combination with diloxanide furoate and dicyclomine to eradicate intestinal and extraintestinal amoebiasis and also asymptomatic cyst passers.

3- Secnidazole (SECNIL)

It is 5-nitroimidazole derivative with properties similar to metronidazole and having longer plasma half-life and administered orally as single dose. It is used in intestinal amoebiasis, hepatic amoebiasis, giardiasis and trichomonal vaginitis.

Side effects include nausea, anorexia, epigastric pain, diarrhoea, skin rash, urticaria, headache and leucopenia.

4- Ornidazole (DAZOLIC)

It is a 5-nitroimidazole derivative with the same antimicrobial profile as that of metronidazole, except that it has a much longer half-life. Readily absorbed from the GI tract, widely distributed in body tissues and fluids including the CSF and metabolized in the liver. It is excreted mainly in the urine as conjugates and to a lesser extent in faeces.

Adverse effects include nausea, skin rash, abdominal pain and headache.

It is indicated in giardiasis, severe hepatic and intestinal amoebiasis, trichomoniasis of urogenital tract and bacterial vaginosis.

5- 8-HYDROXYQUINOLINES

Diiodohydroxyquinoline, iodochlorohydroxyquin are effective against *E. histolytica, Trichomonas and Giardia*.

Diiodohydroxyquinoline is directly amoebicidal. It has activity against motile and cystic forms. It kills cyst forming trophozoites in intestine but has no tissue amoebicidal action. It is ineffective in extraintestinal amoebiasis. It is also effective in cyst passing patients. Diiodohydroxyquinoline is partly and irregularly absorbed from the GI tract. Metabolised in liver and excreted in urine as glucuronide and sulfate conjugates.

Adverse effects include nausea, diarrhoea, abdominal discomfort, headache and goitre (so contraindicated in patients with intolerance to iodine). Prolonged use of iodochlorohydroxyquin causes subacute myelooptic neuropathy (SMON).

They are indicated in *giardiasis, trichomonas vaginitis, intestinal amoebiasis* and *amoebic colitis*.

6- Chloroquine

It kills trophozoites of E. histolytica and because of its selective concentration in liver, **it is used** in the treatment of hepatic amoebiasis concurrently or immediately after metronidazole for complete cure. It is not effective in amoebic dysentery and in cyst passers.

7- Emetine derivatives

Emetine and **dehydroemetine (**TILEMETIN) are natural alkaloid obtained from Cephaelis ipecacuanha and synthetic analog respectively. They are effective against tissue trophozoites of E. histolytica. It has no effect on cysts but effective in amoebic liver abscess also. **It acts by inhibiting protein synthesis by arresting intraribosome translocation of tRNA-amino acid complex**. Dehydroemetine is less toxic than emetine and very effective drug for tissue amoebiasis. It is more rap idly eliminated from the body than emetine.

Adverse effects include nausea, vomiting, diarrhoea, myalgias and because of its serious side effects including cardiac arrhythmia, CHF and hypotension, they have been almost completely replaced by metronidazole.

8- Diloxanide furoate (FURAMIDE)

It is a dichloroacetamide derivative, very effective luminal amoebicide. Used alone for cyst passers or usually with metronidazole for other forms of amoebic infections. **It directly kills trophozoites**. It has no antibacterial activity. After oral administration it is rapidly absorbed and excreted rapidly in urine as glucuronide conjugate.

Adverse effects include flatulence, nausea, vomiting, anorexia and pruritus.

It is mainly indicated in mild intestinal amoebiasis and asymptomatic cyst passers. **It is also used** in combination with tinidazole (TINIBA DF) and metronidazole (ENTAMIZOLE) in the treatment of intestinal amoebiasis, hepatic amoebiasis and other systemic diseases due to E. histolytica.

9- Furazolidone (FUROXONE)

It is effective against gram negative bacilli e.g. Shigella, Salmonella and also effective against Trichomonas and Giardia. **It is indicated** in bacterial enteritis, diarrhoea, giardiasis and bacillary dysentery. **Adverse effects** include nausea, vomiting, headache and dizziness.

10- Paromomycin

It is an aminoglycoside antibiotic used only as luminal amoebicide and has no effect against extra intestinal amoebic infections. It is less toxic than other agents, but it

should be used cautiously in patients with significant renal disease and with gastrointestinal ulcer.

LEISHMANIASIS

Visceral leishmaniasis (kalaazar) is caused by Leishmania donovani and transmitted by Phlebotomus sandfly. In human being, it is found intracellularly within macrophages in the nonflagellate form. The important drugs used in leishmaniasis are pentamidine, sodium stibogluconate, antifungal antibiotics (amphotericin B and ketoconazole) and antigout agent (allopurinol).

1- PENTAMIDINE

Pentamidine is an aromatic diamidine formulated as an isoethionate salt used parenterally (4 mg/kg IM or slow IV injection). It has activity against *trypanosomatid protozoans* and against *Pneumocystis carinii*. It probably interacts with kinetoplast DNA and inhibits topoisomerase II. It is used in the treatment of pneumocystosis (pulmonary and extrapulmonary disease caused by P. carinii), African trypanosomiasis (disease caused by *Trypanosoma brucei*) and leishmaniasis. Systemic pentamidine is highly toxic and can lead to severe hypotension, tachycardia, dyspnea, dizziness, hypoglycemia. Other adverse effects are skin rash, metallic taste, gastrointestinal symptoms, thrombocytopenia and cardiac arrhythmias.

2- SODIUM STIBOGLUCONATE

It is pentavalent antimonial. It inhibits–SH dependent enzymes and block glycolytic & fatty acid oxidation pathways. It is rapidly absorbed after IM injection and excreted unchanged in urine. Used in cutaneous and visceral leishmaniasis. It is given parenterally (20 mg/kg/day IM/IV) for three weeks in cutaneous leishmaniasis and for four weeks in visceral and mucocutaneous disease.

Adverse effects include metallic taste headache, fever, rash, myalgia and ECG changes.

TRYPANOSOMIASIS

It is caused by genus Trypanosoma which is characterized by skin eruptions, sustained fever, lethargy and lymphadenitis, progressive brain dysfunction. Apart from **imidazole derivative** e.g. **metronidazole**, **tinidazole**, **nimorazole** etc. and other agents such as hydroxyquinolines, iodine preparation (povidoneiodine) and antifungal antibiotics e.g. clotrimazole (used mainly as vaginal pessaries), there are some other compounds which are mainly used in the treatment of trypanosomiasis. They are:

1- Suramin

It is a sulfated napthylamine and used as first line therapy for early hemolymphatic African trypanosomiasis (caused by T. brucei gambiense). It has very tight protein binding and having short initial half-life but terminal half life is about 50 days and is excreted by kidney.

It is also used for chemoprophylaxis against African trypanosomiasis.

Adverse effects include nausea, vomiting, fatigue, dermatitis, fever, photophobia, haemolytic anaemia, albuminuria and hematuria.

2- Melarsoprol

Chemically it is trivalent arsenical used for advanced CNS African trypanosomiasis. It is administered IV in propylene glycol and after administration it is rapidly excreted. It is highly toxic and used only in advanced trypanosomiasis when no alternative is there.

Adverse effects include vomiting, fever, abdominal pain, renal and cardiac disease and encephalopathy characterized by cerebral edema, seizures, coma (even death).

3- Eflornithine

It is an inhibitor of ornithine decarboxylase and is used as second line therapy for advanced CNS African trypanosomiasis. After oral or IV administration, peak plasma level is reached rapidly and elimination half-life is approximately three hours. **It is effective** against advanced T. *brucei gambiense* infection.

Adverse effects include vomiting, diarrhoea, leukopenia, thrombocytopenia, anaemia and seizures.

4- Nifurtimox

Chemically it is nitrofuran, used for American trypanosomiasis which is commonly known as ‘Chagas disease.’ After oral administration, it is well absorbed and plasma half-life is about three hours.

Adverse effects include nausea, vomiting, fever, rash, abdominal pain, neuropathies and seizures.

TRICHOMONIASIS

It is caused by Trichomonas vaginalis and is mainly associated with vulvovaginitis which is characterized by greenish yellow and cheesy vaginal discharge. The various agents used in trichomoniasis are metronidazole, tinidazole and secnidazole which are already described earlier. They produce 100% cure. **Other protozoal** infection is giardiasis which is caused by Giardia lamblia and the drug of choice in its treatment are imidazole derivatives.

Reference:

Singh, Surender. ***Pharmacology for dentistry***. New Age International, 2007.